IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE TRICOR DIRECT PURCHASER ANTITRUST LITIGATION	C.A. No. 05-340 (SLR) (Consolidated)
THIS DOCUMENT RELATES TO: ALL ACTIONS	
IN RE TRICOR INDIRECT PURCHASER ANTITRUST LITIGATION	C.A. No. 05-360 (SLR) (Consolidated)
THIS DOCUMENT RELATES TO: ALL ACTIONS	

REDACTED / PUBLIC VERSION

DECLARATION OF RUSSELL A. CHORUSH

Chimicles & Tikellis, LLP
Pamela S. Tikellis (#2172)
A. Zachary Naylor (#4439)
P.O. Box 1035
One Rodney Square
Wilmington, DE 19899
Tel: 302-656-2500
Fax: 302-656-9053

ADDITIONAL COUNSEL ON SIGNATURE PAGE

Date: June 9, 2008

CONTAINS HIGHLY CONFIDENTIAL INFORMATION: SUBJECT TO PROTECTIVE ORDER

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DECLARATION OF RUSSELL A. CHORUSH

I, Russell A. Chorush, submit this Declaration pursuant to 28 U.S.C. § 1746 and declare as follows:

1. I have personal knowledge of facts stated in this Declaration, and if called upon as a witness, could and would testify competently thereto.

2. Attached as Exhibit A is a true and correct copy of United States Patent No. 4,895,726.

3. Attached as Exhibit B is a true and correct copy of a translated document bearing Bates numbers TriCor023308-310.

4. Attached as Exhibit C is a true and correct copy of excerpts from the deposition of Dr. Arthur Goldberg.

5. Attached as Exhibit D is a true and correct copy of an expert report submitted by Mr. Joseph Colaianni.

6. Attached as Exhibit E is a true and correct copy of an expert report submitted by Dr. Arthur Goldberg.

7. Attached as Exhibit F is a true and correct copy of excerpts from the deposition of Mr. Joseph Colaianni.

8. Attached as Exhibit G is a true and correct copy of a document from the reexamination of United States Patent No. 4,895,726.

9. Attached as Exhibit H is a true and correct copy of a document from the reexamination of United States Patent No. 4,895,726.

10. Attached as Exhibit I is a true and correct copy of excerpts from the deposition of Mr. Philippe Reginault.

I declare under penalty of perjury that the foregoing is true and correct.

Executed June 2, 2008

Russell A. Chorush

EXHIBIT A

United States Patent [19]

Curtet et al.

[11] **Patent Number: 4,895,726**

[45] **Date of Patent: Jan. 23, 1990**

[54] **NOVEL DOSAGE FORM OF FENOFIBRATE**

[75] Inventors: **Bernard Curtet**, Marsanny la Cote; **Eric Teilland**, Talant; **Philippe Reginault**, Fontaine les Dijon, all of France

[73] Assignee: **Fournier Innovation et Synergie**, Paris, France

[21] Appl. No.: **299,073**

[22] Filed: **Jan. 19, 1989**

[30] **Foreign Application Priority Data**

Feb. 26, 1988 [FR] France 88 02359

[51] **Int. Cl.**[4] **A61K 9/64**

[52] **U.S. Cl.** **424/456**; 424/452; 424/458

[58] **Field of Search** 424/456, 452, 458

[56] **References Cited**

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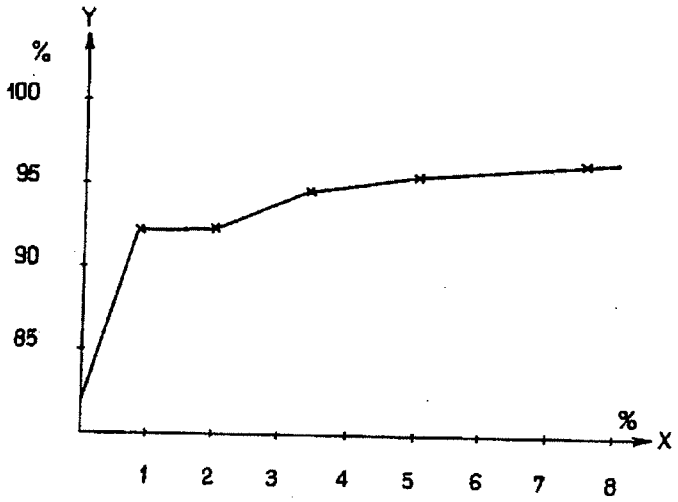
Primary Examiner—Ellis P. Robinson
Assistant Examiner—Leon R. Horne
Attorney, Agent, or Firm—Fleit, Jacobson, Cohn, Price, Holman & Stern

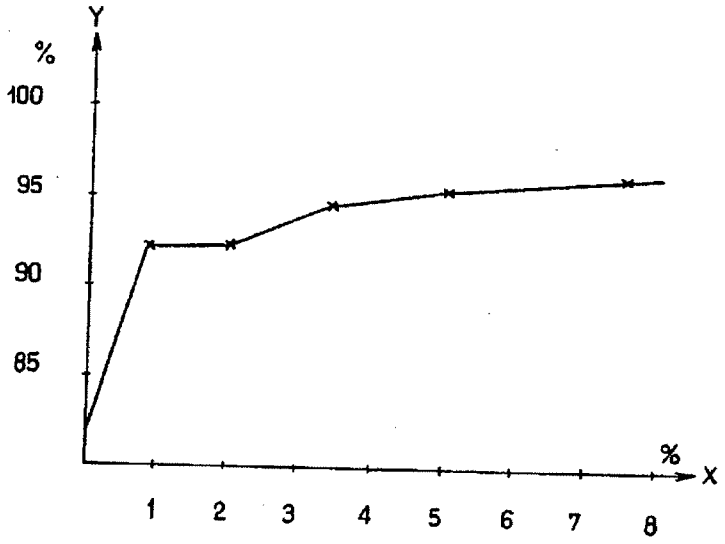
[57] **ABSTRACT**

The present invention relates to a novel dosage form of fenofibrate containing fenofibrate and a solid surfactant which have been co-micronized.

It also relates to the method for the preparation of this dosage form and its use for improving the bioavailabity in vivo.

12 Claims, 1 Drawing Sheet

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NOVEL DOSAGE FORM OF FENOFIBRATE

The present invention relates to a novel dosage form of fenofibrate. It relates more precisely to a therapeutic composition containing fenofibrate and ensuring an improved bioavailability, and to a method for the preparation of this composition.

Fenofibrate (international common name), which is recommended in the treatment of hyperlipidemia and hypercholesterolemia, corresponds to the nomenclature isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropionate. The customary adult dosage is three gelatin capsules per day, each containing 100 mg of fenofibrate.

For the patient's comfort, it is advantageous to try and find a dosage form which has to be taken only once a day and whose psychological effect is identical to that obtained when multiple doses are taken. A gelatin capsule containing 300 mg of fenofibrate has therefore been proposed, the dosage recommended in this case being only one administration per day.

However, it is possible to try and improve the dosage form still further. It is known, in fact, that the bioavailability of fenofibrate is not equal to 100%. It is therefore desirable to develop a dosage form in which the bioavailability of the fenofibrate is improved and which can be administered only once a day.

It is known that the micronization of an active principle is capable of improving the dissolution of the said active principle in vivo, and hence its bioavailability. It is also known that the addition of a surfactant excipient to a formulation of an active principle is capable of improving the absorption and consequently the bioavailability of the said active principle.

It has now been discovered that the co-micronization of fenofibrate and a solid surfactant (i.e. the micronization of an intimate mixture of fenofibrate and a solid surfactant) makes it possible to improve the bioavailability of the fenofibrate to a significantly greater extent than that which would be achieved either by adding a surfactant, or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronized fenofibrate and surfactant.

The present invention therefore proposes a novel therapeutic composition, presented in the form of gelatin capsules, which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, the said composition containing fenofibrate and a solid surfactant which have been co-micronized.

The recommended amount of fenofibrate is about 200 mg per therapeutic unit.

The surfactant will be selected from solid surfactants so that it can be co-micronized with the fenofibrate. An alkali metal sulfate of lauryl alcohol, for example sodium lauryl-sulfate (alternative name: sodium dodecyl-sulfate), will be preferred. The recommended amount of sodium lauryl-sulfate will be between 0.5% and 7% by weight, relative to the total weight of the formulation. The weight ratio surfactant/fenofibrate will advantageously be between about 0.75/100 and 10.5/100.

The co-micronization of the fenofibrate and the solid surfactant will advantageously be carried out in an accelerated air-jet mill until the powder obtained is such that the mean particle size is less than 15 μm, preferably less than 10 μm and particularly preferably less than 5 μm.

To obtain a powder which can be formulated into gelatin capsules, conventional filling, dispersing and

flow-enhancing excipients, for example lactose, starch, polyvinylpyrrolidone and magnesium stearate, may be added to the co-micronizate of fenofibrate and solid surfactant.

According to the invention, a method for the preparation of a therapeutic composition containing fenofibrate and a solid surfactant is recommended which comprises:

(i) intimately mixing and then co-micronizing the fenofibrate and the solid surfactant,

(ii) adding lactose and starch to the mixture obtained,

(iii) converting the whole to granules in the presence of water,

(iv) drying the granules until they contain no more than 1% of water,

(v) grading the granules,

(vi) adding polyvinylpyrrolidone and magnesium stearate to the graded granules, and

(vii) filling gelatin capsules with the mixture obtained in stage (vi).

The invention will be understood more clearly from the description of the Preparative Examples which follow and from the description of the results obtained in comparative tests, which show that the invention is non-obvious.

PREPARATION I

For 100,000 gelatin capsules, each weighing 350 mg and containing 200 mg of fenofibrate, the amounts of products used are as follows:

fenofibrate	20.0 kg
sodium lauryl-sulfate	0.7 kg
α-lactose monohydrate	10.1 kg
pregelatinized starch	3.0 kg
crosslinked polyvinyl-pyrrolidone	0.7 kg
magnesium stearate	0.5 kg

The fenofibrate/sodium lauryl-sulfate mixture is co-micronized in an air-jet micronizer to give a powder with a median partizle size of 3 μm. The lactose and the starch are then added to this powder and the whole is converted to granules in the presence of 8.9% of distilled water, relative to the total weight of the mixture. The granules obtained in this way are dried for one day at 50° C. and then graded so as to retain only the particles with sizes less than or equal to 1000 μm. The polyvinylpyrrolidone and the magnesium stearate are then added and the whole is mixed until homogeneous. The powder obtained is used to fill size 1 gelatin capsules on an automatic machine with the compression set to a maximum of 150N.

PREPARATION II

The procedure indicated in Preparation I is followed using a fenofibrate/sodium lauryl-sulfate mixture with a median particle size of 6–7 μm.

PREPARATION III

For 100,000 size 1 gelatin capsules, each weighing 297 mg and containing 200 mg of active principle, the amounts of products are as follows:

fenofibrate	20.0 kg
sodium lauryl-sulfate	0.3 kg
α-lactose monohydrate	6.8 kg
pregelatinized starch	1.5 kg

-continued

crosslinked polyvinyl-pyrrolidone	0.6 kg
magnesium stearate	0.5 kg

The procedure is analogous to that used for Preparation I, the co-micronization of the fenofibrate/sodium lauryl-sulfate mixture being such that the median particle size is 6–7 μm and the granulation being carried out in the presence of 10% of distilled water, relative to the weight of the fenofibrate/sodium lauryl-sulfate/lactose/starch mixture.

PREPARATION IV

Following a procedure analogous to that described in Preparation I, using a co-micronized mixture of fenofibrate and sodium lauryl-sulfate with a median particle size of 6–7 μm, the formulations collated in Table I below were prepared:

TABLE I

COMPOSITION (in mg) PER GELATIN CAPSULE

INGREDIENT	FORMULATION A	B	C	D	E	F
Fenofibrate	200	200	200	200	200	200
Na lauryl-sulfate	0	3	7	12	17.5	26.5
Lactose	108	105	101	95	90.5	83.5
Starch	30	30	30	30	30	30
Polyvinylpyrrolidone	7	7	7	7	7	7
Mg stearate	5	5	5	5	5	5
Percentage of Na lauryl-sulfate	0	0.86	2	3.4	5	7.53

Taking these formulations, the dissolution curve shown in FIG. 1 was plotted, the percentage of dissolved fenofibrate (Y) being given as a function of the percentage of sodium lauryl-sulfate contained in the formulation (X). The dissolution kinetics are determined, as specified in the European Pharmacopoeia, using a rotating-vane apparatus, the eluent consisting of water and 0.1M sodium lauryl-sulfate. The fenofibrate is determined by UV spectrophotometry at 282 nm. The curve in FIG. 1 is given by the values obtained after 20 minutes.

These results show that 82% of fenofibrate is dissolved at a sodium lauryl-sulfate concentration of 0%, 87% of fenofibrate is dissolved at a concentration of 0.5%, 92% of fenofibrate is dissolved at a concentration of 1% and a maximum dissolution of 95 to 96% of fenofibrate is obtained as from a sodium lauryl-sulfate concentration of 4%.

The dissolution curves were also plotted, in a continuous-flow cell with a flow rate of 20 ml/min of 0.1M sodium lauryl-sulfate, for formulations containing co-micronized fenofibrate and sodium lauryl-sulfate (NaLS), by comparison with micronized fenofibrate and with formulations obtained by intimately mixing separately micronized fenofibrate and lauryl-sulfate. The comparison is made by means of T 50%, i.e. the time required for 50% of the fenofibrate to dissolve. The results obtained are collated in Table II below:

TABLE II

VALUE OF THE T 50% TIMES (in minutes)

INGREDIENTS	A	B	C
Micronized pure fenofibrate	37.165	37.165	0
Fenofibrate + 1% of NaLS	18.01	8.62	−52.14
Fenofibrate + 3% of NaLS	23.75	12.68	−46.61
Fenofibrate + 5% of NaLS	20.35	11.425	−43.86
Fenofibrate + 7% of NaLS	14.5	10.76	−25.79

Notes
A mixture of micronizates
B co-micronization of the mixture of ingredients
C variation $\frac{B-A}{A} \times 100$ (in %)

These results show that the T 50% of the fenofibrate is very significantly reduced (hence the dissolution rate of the fenofibrate is very significantly increased) when the fenofibrate and the sodium lauryl-sulfate are co-micronized, compared with the mixture of separately micronized fenofibrate and sodium lauryl-sulfate and compared with fenofibrate alone.

The dissolution rate of fenofibrate is correlated with the bioavailability of fenofibrate, which increases with the dissolution rate. The above results shown that it was not within the understanding of those skilled in the art to prepare a therapeutic composition characterized by the co-micronization of fenofibrate and a solid surfactant.

These results have been confirmed in clinical trials. Fenofibrate was administered to groups of healthy subjects, (a) in the form of a single administration (1 gelatin capsule) of 300 mg of non-micronized fenofibrate (marketed under the tradename "LIPANTHYL 300") and (b) in the form of a single administration of 200 mg of co-micronized fenofibrate obtained according to Preparation III described above. Blood samples are taken from the subjects at regular intervals and one of the active metabolites—2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionic acid—is determined. The curve showing the concentration of this metabolite as a function of time is plotted and the area under the curve [AUC(0-∞)], expressed in mg/l.h, is calculated.

The results obtained are shown in Table III below:

TABLE III

BIOAVAILABILITY PARAMETER	FENOFIBRATE 200 mg (1)	FENOFIBRATE 300 mg (2)
AUC(0-∞)(mg/l.h)	174.15 ± 48.67	168.85 ± 57.68
C max (m/l)	10.86 ± 2.13	10.39 ± 2.89
t max (h)	5.97 ± 2.50	5.52 ± 1.70
t ½ (h)	15.13 ± 4.27	17.79 ± 8.77

Notes
(1) co-micronized fenofibrate (200 mg)
(2) non-micronized fenofibrate (300 mg)

The results in Table III show that there is not a statistically significant difference between the in vivo bioavailability of 200 mg of co-micronized fenofibrate according to the invention and 300 mg of non-micronized fenofibrate (which is currently the preferred dosage form for a single daily administration). In other words, co-micronized fenofibrate at a 200 mg dose is bioequivalent to non-micronized fenofibrate at a 300 mg dose.

According to another aspect of the invention, a method for improving the bioavailability of fenofibrate in vivo is recommended, the said method comprising co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by

micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 μm and preferably less than or equal to 5 μm.

What is claimed is:

1. A therapeutic composition, which is presented in the form of gelatin capsules and which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant, wherein the mean particle size of said co-micronized mixture is less than 15 μm.

2. The therapeutic composition according to claim 1 wherein the weight ratio surfactant/fenofibrate is between about 0.75/100 and 10.5/100.

3. The therapeutic composition according to claim 1 wherein the amount of fenofibrate is equal to 200 mg per therapeutic unit.

4. The therapeutic composition according to claim 1, wherein the solid surfactant is sodium lauryl-sulfate.

5. The therapeutic composition according to claim 4, wherein the amount of sodium lauryl-sulfate is between 0.5 and 7% by weight, relative to the total weight of the formulation.

6. The therapeutic composition according to claim 1, wherein said mean particle size is less than or equal to 10 μm and said solid surfactant is sodium lauryl-sulfate.

7. The therapeutic composition according to claim 1, which also contains excipients such as dispersants, fillers and flow enhancers.

8. A method for the manufacture of a therapeutic composition according to claim 1, which comprises:

(i) intimately mixing and then co-micronizing the fenofibrate and a solid surfactant,

(ii) adding lactose and starch to the mixture obtained,

(iii) converting the whole to granules in the presence of water,

(iv) drying the granules until they contain no more than 1% of water,

(v) grading the granules,

(vi) adding polyvinylpyrrolidone and magnesium stearate, and

(vii) filling gelatin capsules.

9. The method according to claim 8, wherein the mean particle size of the co-micronized fenofibrate and sodium lauryl-sulfate is less than 15 μm.

10. A method for improving the bioavailability of fenofibrate in vivo, which comprises co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 μm.

11. A method for treatment of hyperlipidemia or hypercholesterolemia comprising orally administering the therapeutic composition of claim 6 to a patient.

12. The method of treatment of claim 11, wherein said particle size is less than or equal to 5 μm.

* * * * *

US004895726B1

(12) REEXAMINATION CERTIFICATE (4423rd)

United States Patent
Curtet et al.

(10) Number: US 4,895,726 C1
(45) Certificate Issued: Aug. 28, 2001

(54) DOSAGE FORM OF FENOFIBRATE

(75) Inventors: **Bernard Curtet**, Marsanny la Cote; **Eric Teillaud**, Talant; **Philippe Reginault**, Fontaine les Dijon, all of (FR)

(73) Assignee: **Fournier Industrie et Sante** (FR)

Reexamination Request:
No. 90/005,586, Dec. 13, 1999

Reexamination Certificate for:
Patent No.: **4,895,726**
Issued: **Jan. 23, 1990**
Appl. No.: **07/299,073**
Filed: **Jan. 19, 1989**

(30) **Foreign Application Priority Data**

Feb. 26, 1988 (FR) 88 02359

(51) **Int. Cl.**[7] **A61K 9/64**; A61K 9/48; A61K 9/54; A61K 31/235

(52) **U.S. Cl.** **424/456**; 424/452; 424/458; 514/543

(58) **Field of Search** 424/456, 452, 424/458; 514/543

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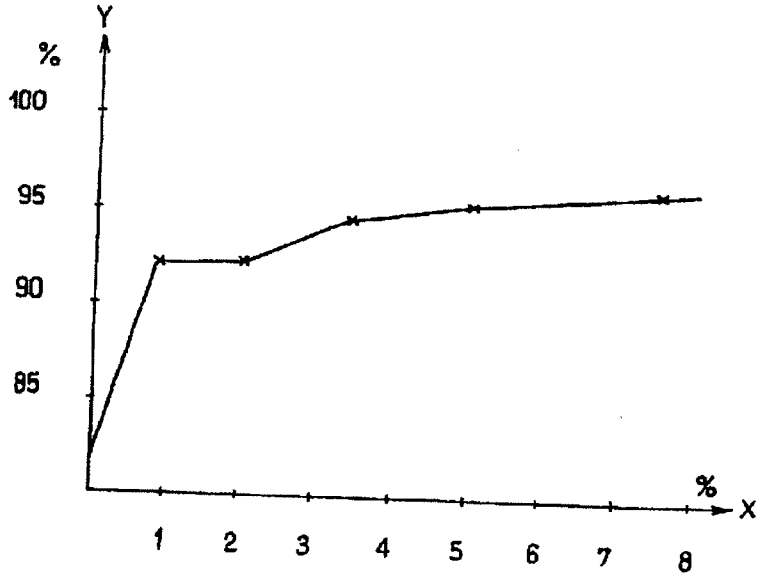
(List continued on next page.)

Primary Examiner—Thurman K. Page

(57) **ABSTRACT**

The present invention relates to a novel dosage form of fenofibrate containing fenofibrate and a solid surfactant which have been co-micronized.

It also relates to the method for the preparation of this dosage form and its use for improving the bioavailabity in vivo.



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REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims 1–12 is confirmed.

* * * * *

EXHIBITS B-F

REDACTED

EXHIBIT G

Re-exam
TC 1600
CM1 11D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Reexamination of

Bernard CURTET et al

Patent No. 4,895,726

Reexam Control No. 90/005,586

Filed: December 13, 1999

For: NOVEL DOSAGE FORM OF FENOFIBRATE

Group Art Unit 1615

Examiner Venkat

6/ Response to Reexam Order

RESPONSE UNDER 37 CFR §1.530(b)

Bet
12-19-00

Asst. Commissioner of Patents
Washington, D.C. 20231

Sir:

This is in response to the Order mailed February 24, 2000 granting the request for reexamination.

The Examiner's Comments In Granting Reexamination

The Examiner states a substantial new question of patentability affecting claims 1-12 of the Curtet et al patent, 4,895,726, is raised by the request for reexamination. More specifically, the Examiner states that consideration of the Boullay article along with certain admissions in the Curtet et al patent specification raises a substantial new question of patentability as to all of the claims of the Curtet et al patent. The Examiner further states there is a substantial likelihood that a reasonable examiner would consider certain teachings in the Boullay paper important in deciding whether or not the claims are patentable. Accordingly, the Examiner concludes the article raises a substantial new question of patentability which has not been decided in previous examination of the Curtet et al patent.

Background of the Invention

A. Technical Problem

Prior to the present invention, the specialty form used for fenofibrate was a daily gelatine capsule containing 300 mg of fenofibrate. The relatively poor bioavailability of fenofibrate was known and research was carried out in order to develop a galenic form which would exhibit an improved bioavailability vis-a-vis the 300 mg form.

Two research routes were followed.

1. Dissolving fenofibrate. Several solvents such as certain triglycerides and edible oils (for instance, peanut oil, olive oil, palm oil, etc.) were tested without achieving any satisfactory result.
2. Improving fenofibrate absorption through decrease in particle size. The simple micronization of fenofibrate did not give any satisfactory result.

B. Surfactant

Penofibrate being hydrophobic, it was thought to add a surfactant to improve the wettability of fenofibrate.

Sodium laurylsulfate was selected because (i) it is acceptable from a pharmaceutical point of view, and (ii) it was thought to be suitable to improve the fenofibrate wettability.

A first difficulty arose: the mixture of micronized fenofibrate and sodium laurylsulfate was not satisfactory, for micronized fenofibrate is a very light powder whereas sodium laurylsulfate is more dense than micronizied fenofibrate. It was difficult to provide a homogeneous mixture and there were some risks of explosion of fenofibrate.

C. Solution of the Problem

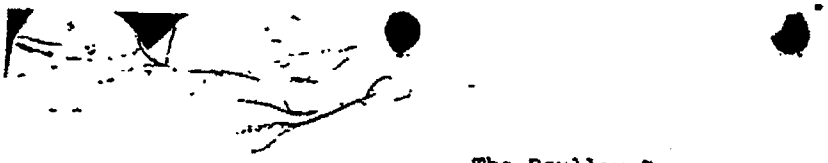
Co-micronization of fenofibrate with sodium laurylsulfate was tested to overcome the above difficulty regarding the lack of homogeneity. An acceptable form was obtained and with it an increase in the dissolution rate, which was looked for, was observed vis-a-vis (i) micronized fenofibrate and (ii) the micronized fenofibrate/sodium laurylsulfate mixture.

The Curtet et al Patent Claims

Independent claim 1 of the Curtet et al patent is directed to a therapeutic composition of gelatin capsules containing a co-micronized mixture of particles of fenofibrate and a solid surfactant. The mean particle size of the co-micronized mixture is less than 15 μm. Independent claim 10 is directed to a method for improving the bioavailability of fenofibrate in vivo, which includes co-micronizing fenofibrate and a solid surfactant until the particle size is less than 15 μm. The remaining claims are all dependent.

The Admitted Prior Art

The Examiner has referred to the admitted prior art in the Curtet et al patent specification in the last paragraph on page 2 of the action. In considering these admissions, the Examiner is respectfully requested to take these admissions in the overall context of the Curtet et al patent disclosure and discovery, namely, that the co-micronization of fenofibrate and a solid surfactant (i.e., the micronization of an intimate mixture of fenofibrate and a solid surfactant) makes it possible to improve the bioavailability of the fenofibrate to a significantly greater extent than that which would be achieved either by adding a surfactant, or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronizied fenofibrate and surfactant.



The Boullay Paper

While it is agreed a substantial new question of patentability is presented, the Boullay paper does not anticipate the claims of the Curtet et al patent and does not render the claims of the Curtet et al patent obvious, either alone or in any reasonable combination with the admitted prior art. The Boullay paper does not disclose or suggest the co-micronization of fenofibrate and a solid surfactant. Moreover, the Boullay paper does not suggest a particle size of less than 15 μm for the mixture of co-micronized fenofibrate and surfactant.

A. Boullay's Reservations

The Boullay paper specifically teaches that the increase in dissolution is not predictable for all formulations (pages 9-10 of the translation). While the Boullay paper might suggest experimentation with co-micronization, it is clear the author has many reservations about the technique and its broad applicability. Given these reservations, those skilled in the art would hardly have a reasonable expectation of success in applying the co-micronization technique to fenofibrate in particular.

B. Boullay's Results

The Boullay paper recites that good results were obtained when co-micronization of an active principle/surfactant or active principle/surfactant/carbohydrate mixture took place. To be precise, Boullay states: "We have carried out several studies on this aspect, with very convincing results" (translation, page 9, third paragraph below Figure 5). However, since those ("very convincing") results are not provided, they cannot be reproduced and checked. The pharmaceutically active principle is not specifically disclosed. The sole information which is given is the particle size of the active principle. More particularly, the

assayed active principle is only characterized by its particle size, namely: (i) between 3 and 100 μm with a median of 25 μm before micronization or co-micronization, and (ii) between 0.7 and 15 μm with a median of 3.5 μm after micronization or co-micronization (translation, page 6, last paragraph).

C. Figure 5

Figure 5 of the Boullay paper (page 9 of the translation), shows the dissolution (%/h) of a raw product (curve 1), the dissolution of the same product after micronization (curve 2) and after co-micronization with 2% of surfactant (curve 3). However, the identity of the raw product is not mentioned in the article. Figure 5 is idealistic and certainly not characteristic of all products.

D. Lactose

In the Boullay article, it is suggested to co-micronize a mixture of three compounds: the active principle, the surfactant and a carbohydrate. Unlike the Boullay teaching, lactose does not intervene in the co-micronization in the present invention. It is used in the present invention (see steps (ii)-(iii) of claim 8 and steps (ii)-(iii) in column 2, lines 11-13), after the co-micronization of the fenofibrate/sodium laurylsulfate mixture, for granulation purposes with starch (column 2, lines 42-45).

E. Particle Size

The fact of diminishing the particle size leads to an increase in the contact surface with gastrointestinal liquids and promotes the dissolution of fenofibrate and hence its bioavailability. The air-jet micronizing technique, as recommended by Boullay and recited in the Curtet et al patent (see column 2, lines 40-42), gives a median particle size of 3-7 μm.

Comparative Tests

A. The Curtet Declaration

The comparative data as provided in Table A of the attached Curtet Declaration clearly establishes that two assayed fibrates, namely, bezafibrate and gemfibrozil, exhibit different dissolution rates as a function of the micronization technique. Micronized alone, each of these two fibrates have a dissolution rate higher than the corresponding co-micronized bezafibrate/surfactant or gemfibrozil/surfactant mixture, wherein the surfactant is sodium laurylsulfate. This shows that (i) bezafibrate and gemfibrozil can indeed be each micronized alone, but that (ii) their co-micronization each with a solid surfactant such as sodium laurylsulfate induces a decrease in the dissolution rate. In short, while improving the dissolution rate is the goal, co-micronization of bezafibrate or gemfibrozil with a surfactant is useless. On the other hand, co-micronization of fenofibrate with a surfactant, unlike bezafibrate and gemfibrozil, unexpectedly gives an increase in the dissolution rate.

B. The Patent Specification

The Examiner's attention is also directed to the comparative tests set forth in the Curtet et al patent. The results set forth in Table II show that the T 50% of the fenofibrate is very significantly reduced (whereby the dissolution rate of the fenofibrate is very significantly increased) when the fenofibrate and the sodium laurylsulfate are co-micronized, compared with the mixture of separately micronized fenofibrate and sodium laurylsulfate and compared with fenofibrate alone (Table II and column 4, lines 15-21).

The results in Table III show that there is not a statistically significant difference between the <u>in vivo</u> bioavailability of 200 mg of co-micronized fenofibrate according to

the invention and 300 mg of non-micronized fenofibrate (which was the preferred dosage form for a single daily administration). In other words, co-micronized fenofibrate at a 200 mg dose is bioequivalent to non-micronized fenofibrate at a 300 mg dose (Table III and column 4, lines 55-63).

CONCLUSION

In view of the above remarks, it is submitted that while a substantial new question of patentability exists, the claims in the Curtet et al patent are patentable over the Boullay article and the admitted prior art.

37 CFR 1.565(a)

Attached hereto is a copy of a complaint filed by Abbott Laboratories, in the United States District Court, Northern District of Illinois, Eastern Division, involving U.S. Patent No. 4,895,726. The civil action number is OOC 2141.

The Commissioner is hereby authorized to charge any fees due in connection with the present Response to Deposit Account 06-1358.

Respectfully submitted,

JACOBSON, PRICE, HOLMAN & STERN, PLLC

By D Douglas Price Reg. No. 24,514
for John C. Holman, Reg. No. 22,769

400 7th Street, N.W.
Washington, D.C. 20004
(202) 638-6666
Atty. Dkt. P50922US1

Enclosures:
1) Complaint OOC 2141
2) Declaration by Dr. Curtet

EXHIBIT H

JD

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D C 20231

JACOBSON PRICE HOLMAN AND STERN PLLC
400 SEVENTH STREET N W
WASHINGTON, DC 20004-2201

In re Reexamination Proceeding:
Bernard Curtet
Serial No.: 90/005,586
Filed: December 13, 1999
Patent No: 4,895,726

: EXTENSION OF TIME

This is in response to applicant's request, filed April 6, 2001, to accept a revised Patent Owner's reply to the order granting reexamination.

A request for reexamination was filed on December 13, 1999, and an order granting reexamination issued on February 24, 2000, setting a two month period for Patent Owner to provide a statement as provided for under 37 CFR 1 550(c). Patent Owner filed a statement on April 24, 2000, which included an affidavit under 37 CFR 1.132 by Bernard Curtet. The statement and subsequent submissions identified ongoing litigation. On April 6, 2001, Patent Owner submitted a request for replacement of the original Patent Owner's statement because of errors discovered therein, especially with respect to the affidavit.

Patent Owners request is granted to the extent that the original statement will remain in the record, but not be considered further in the prosecution of the proceeding. An extension of time sufficient to allow acceptance of the substitute Patent Owners statement is granted *nunc pro tunc*. The examiner will consider only the Patent Owner's statement filed April 6, 2001.

The proceeding will be forwarded to the examiner for further consideration not inconsistent with this decision.

Should there be any questions with regard to this letter please contact William R. Dixon, Jr. by letter addressed to the Director, Group 1600, Washington, DC 20231, or by telephone at (703) 308-3824 or by facsimile transmission at (703) 305-7230.

John Doll
Director, Group 1600

90005586 04-24-01

EXHIBIT I

REDACTED